

cervical nodes were palpable but non tender. The rest of the general examination was normal at this stage.

Swabs from the ulcer for herpes simplex identification using direct fluorescent antibody tests were negative. Bacterial swab from the ulcer base grew only *Staphylococcus aureus*. Vaginal swabs were negative for trichomonas, candida and *Neisseria gonorrhoeae*. Throat swab showed commensal flora only. Syphilis serology was negative and an initial monospot test for glandular fever was negative. A full blood count was normal with a left shift in the neutrophils. ESR was 6 mm in 1 h.

Treatment was commenced with topical lignocaine gel which afforded little relief and a five day course of acyclovir tablets, 200 mg five times a day, was started.

Over the next few days the patient developed more classic symptoms of Epstein-Barr Virus infection with marked generalised lymphadenopathy. Her tonsils became covered in a white exudate and she developed an atypical lymphocytosis in the peripheral blood film. Throat swab for bacterial and other respiratory viruses and mycoplasmas were negative and stool virology for enteroviruses was negative too. Serological testing for EBV using the specific IgM-VCA now gave a positive result, confirming the recent infection with EBV. Herpes Complement Fixation test on paired sera showed no rise in titres over this time, and herpes cultures were negative.

We were interested in this case for a number of reasons. The young girl consistently denied penetrative sexual intercourse or oral-genital contact and yet there was always doubt in the practitioners' minds who saw her that this had to be a primary genital herpes and consequently she was not totally believed. Considerable tension was put on the mother/daughter relationship because of this. One physician who saw her also raised a query of sexual abuse.

The clinical course was also interesting in that the initial symptoms were of marked genital ulceration, rather than the classic glandular fever pharyngitis. This is different from an otherwise similar case reported in 1977¹ where tonsillitis and genital ulceration were the presenting symptoms and the diagnosis of glandular fever was more apparent from the onset. In our patient the initial tests for EBV on a peripheral blood film and monospot test were negative and this confused the picture more and made the presumptive diagnosis of herpes simplex infection more likely.

In retrospect the real clue to the correct diagnosis was given by the colour of the ulcers. The appearance of deep ulcers with vivid purple borders has been described once before in relation to EBV infection.²

Control of pain relief and treatment proved difficult in this patient. She found little relief from the lignocaine gel, which is usually a useful anodyne in herpes simplex infection but she stated she felt much better with the commencement of acyclovir; this may be coincidental but acyclovir is known to have a weak effect against EBV infection.

Genital ulceration secondary to Epstein Barr Virus is not well reported in medical textbooks and to date we could find only two references to this in the past medical literature. Some venereology textbooks do not mention it at all, referring only to the vague term of Lipschutz ulceration.^{3,4} We believe that though primary herpetic vulvitis is very common, this case highlights the need to keep the differential diagnosis much wider, particularly when on taking the history, sexual abstinence is constantly declared. A useful clinical clue to EBV ulceration would appear to be the characteristic dark edge to the ulceration.

G MCKENNA
SHAN EDWARDS
HILARY CLELAND
Christchurch Hospital, Private Bag 4710,
Christchurch, New Zealand

- 1 Brown ZA, Stenchever MA. Genital ulceration and infectious mononucleosis: report of a case. *Am J Obstet Gynaecol* 1977;127:673-4.
- 2 Portnoy J, Ahronheim GA, Ghibu F, et al. Recovery of Epstein Barr virus from genital ulcers. *N Eng J Med* 1984;311:966-8.
- 3 *Sexually Transmitted Diseases. A Textbook of Genitourinary Medicine*. Csonka GW, Oates JK, eds. London: Balliere Tindall, 1990.
- 4 Berlin C. The pathogenesis of the so-called ulcer valvae acutumet. *Acta Dermatol Venerol* 1965;45:221-2.

Accepted for publication 12 April 1994.

Are doctors in genitourinary medicine clinics perceiving the psychological impact of recurrent genital herpes?

The severe psychosocial problems arising in certain patients with recurrent genital herpes infections (HSV) have been well described.¹⁻⁵ These can include depression,^{1,6-8} anger and hostility,⁶⁻⁹ and a lower self-esteem, bringing about feelings of shame and social insecurity.^{1,7-8} Such problems are compounded by the genital location of the infection, the absence of a cure, the latency of the virus, the recurrent nature of the symptoms, and the social stigma that surrounds the disease.¹ A recent study by Carney, *et al*¹⁰ confirmed the view that suppressive acyclovir taken over a twelve months period is an aid to reducing illness concern and anxiety in patients who show emotional dysfunction because of recurrent genital herpes.

The extent to which doctors working in genitourinary (GU) medicine clinics are aware of psychosocial problems associated with genital HSV, is clearly of importance in the provision of effective care. Before any treatment strategy (including the use of acyclovir) can be initiated, the doctor and patient need to be able to communicate about the presence of psychosocial problems. Russell *et al*¹¹ found that the duration of GU doctors' clinical experience influenced their management of patients with recurrent genital herpes.

In particular the likelihood of oral acyclovir being prescribed for either the first or recurrent episode and continuous suppressive treatment was variable.

We have studied the degree to which doctors are able to perceive the psychological impact of genital herpes on patients. This was done by measuring the patients' depression and anxiety levels, and assessing their expectation of what would occur in their consultation. Then the doctors' clinical impression of the patient, and their perception of the patients' psychological problems was recorded. These were compared with the clinical outcome of the consultation.

When we analysed the relationship between expectation and outcome of a consultation, the correlation for those expecting and receiving a genital examination was the strongest. None of the other items—asking about safer sex, general health, relationships or HIV testing, reached this level of significance.

We assessed 30 consultations with patients who had a history of genital herpes. During the consultation, herpes was discussed in 17 cases, which was initiated by the patient in 11 cases. Doctors felt that the daily lives of 76% of these patients were affected by herpes. They prescribed treatment for 10 of the 17 (58.8%). When giving the reason for prescribing, doctors felt that the patient was stressed (80%), depressed because of herpes (70%) or suffering frequent or severe herpes recurrences (60%).

Hospital Anxiety and Depression Scale sub-scores for anxiety and depression were available for 18 patients. Their mean sub-scores were 7.61 for anxiety and 5.22 for depression. Results are shown in the table. A significant relationship was found between lower HAD anxiety score and length of time since last attack (lower score = longer period since last attack).

The doctor's assessment sheet included a linear scale for the assessment of patients current level of anxiety and depression by the doctor. This was compared with the HAD sub-scores. A significant correlation was found between HAD anxiety sub-scores and doctor's assessment, but not for the depression measures.

As all these patients had previously attended the clinic, it is not surprising that they were able to accurately predict when they would have a genital examination. What is surprising is the poor correlation of outcome with other expected elements of the consultation, suggesting a wide variability in routine consultations. Whilst such consultations provide an opportunity for doctor's to discuss related health and emotional issues, they are also constrained by time and length of waiting lists.

Although clinical records were available to the doctors, clearly indicating that thirty patients had documented genital herpes, the doctors initiated a discussion about herpes in only six cases. In 11 cases the patient initiated discussion, and in 13 cases herpes was not discussed at all. It is possible the doctor has

Hospital anxiety and depression scale subscores for patients with recurrent genital herpes

| Anxiety | No of patients | % | Depression | No of patients | % |
|---------|----------------|----|------------|----------------|----|
| 0-7 | 8 | 44 | 0-7 | 13 | 72 |
| 8-10 | 5 | 28 | 8-10 | 2 | 11 |
| > 11 | 5 | 28 | > 11 | 3 | 17 |

A value of 7 or less correlates well with 'non-cases', 8-10 with doubtful cases and 11 or above with true cases.

missed the real concerns of the patient, hidden beneath other reasons for attending.

Whilst some patients appear to be able to adjust to a diagnosis of herpes, and to continue a normal life, others seem to suffer from "herpes syndrome"—a profound psychopathology and a pervasive if not obsessional concern over herpes.¹ As 28% of patients had significant anxiety, and 17% significant depression HAD sub-scores, emotional disturbance appears to exist in this patient group, with anxiety decreasing when a longer time has elapsed between recurrences.

When the doctor's perception of anxiety and depression levels are looked at, it was found that they were adept at identifying patients' anxiety, but not their degree of depression. It may be that anxiety is better expressed, both verbally and non-verbally, than depression. Alternatively, doctors may be aware of the relationship between anxiety and herpes recurrence, but less aware of a relationship with depression.

A vital step in the management of genital herpes is the recognition of the existence of a problem. Our data suggest that improved method to enable both doctor and patient to detect and discuss depression are necessary. Without required training and practice, the benefit of suppressive acyclovir shown by Carney *et al*¹⁰ will remain out of some patients' reach.

L C CASSIDY

M A HOLDER

S E BARTON

Department of Genitourinary Medicine,

J MEADOWS

J CATALAN

Department of Psychological Medicine,
Chelsea & Westminster Hospital, London, UK

Address correspondence to: Dr S Barton, St Stephen's Clinic, 369 Fulham Road, London, SW10 9TH, UK.

- 1 Bierman, SM. Recurrent genital herpes simplex infection: A trivial disorder. *Arch Dermatol* 1985;121:513-7.
- 2 Drob S, Loemer M, Liftshutz H. Genital herpes: The psychological consequences. *British J Med Psychol* 1985; 58:307-15.
- 3 Goldmeier D, Johnson A, Byrne M, Barton S. Psychological implications of recurrent genital herpes. *Genitourin Med* 1988;64:327-30.
- 4 VanderPlate C, Aral S. Review: Psychological aspects of genital herpes virus infection. *Health Psychology* 1987; 6:57-72.
- 5 VanderPlate C, Aral SO, Magder L. The relationship among genital herpes simplex virus, stress and social support. *Health Psychology* 1988;7:159-68.
- 6 Himell K. Genital herpes: the need for counselling. *Journal of Gynecological Nursing* 1981;10:446-50.
- 7 Marks LN, Patrick NH. I think I may have herpes... What should I do? *Occupational Health and Safety* 1983;52: 15-42.

- 8 Lynch JM. Helping patients through the recurring nightmare of herpes. *Nursing* 1982;12:52-7.
- 9 Sacher JB. Coping and living with herpes. *J Am Dental Assoc* 1983;31:261-2.
- 10 Carney R, Ross E, Ikkos G, Mindel A. The effect of suppressive oral acyclovir on the psychological morbidity associated with recurrent genital herpes. *Genitourin Med* 1993;69:457-9.
- 11 Russell JM, Cracknell M, Barton SE, Catalan J. Management of genital herpes by G.U. physicians: does experience or doctors gender influence clinical management. *Genitourin Med* 1993;69:115-8.

Accepted for publication 14 April 1994

Human papillomavirus (HPV) DNA is not detected in the peripheral blood cells of patients with cervical carcinoma

Studies on cervical carcinoma have indicated a strong association between specific strains of human papillomaviruses (HPV), most commonly HPV 16 and 18, and cervical cancer.¹ The interplay between the early region proteins E6, and E7 of these two HPV types and the cellular tumour suppressor genes Rb and p53, has been suggested to be relevant for a malignant potential.² The classical cytological pap smear is the classical way for early detection of malignant or pre malignant cervical lesions. However, attempts have been made to find other parameters, which will allow early detection of lesions with malignant potential, in order to perform rapid therapeutic measures. Since HPV infection may have a malignant potential, detection of HPV DNA was considered important. DNA hybridisation techniques, including the polymerase chain reaction (PCR) have been used for the detection of HPV DNA in dysplastic and malignant lesions.³ Recently, the repeated presence of HPV in cervical smears has been suggested to be an important predictive factor for the progression of cervical carcinoma. In addition, in some patients suffering from HPV positive urogenital infections HPV DNA could be detected in the patients' peripheral blood cells (PBL).⁴

The aim of this study was to identify if HPV could be detected in the PBLs of cervical cancer patients, and to determine if this presence could be correlated with the prognosis.

Forty-five patients who had been treated or were presently suffering from a cervical carcinoma were included in this study and their status of disease listed in the table. In parallel

these patients were included in a study concerning the correlation of cervical carcinoma and HLA antigens, to be published elsewhere. Genomic DNA was prepared by digesting 8 ml blood (collected in tubes containing EDTA to avoid coagulation) with proteinase K (Boeringer Mannheim) at 42°C overnight and then salted-out with 6M NaCl according to Miller *et al.*⁵ This procedure removed the EDTA. For each PCR reaction approximately 500 ng of DNA, corresponding to approximately 10⁵ cells was used. A nested general primer two step PCR was performed with the general primer pairs My11/My09 and GP5/GP6 located within the HPV type 16 L1 region as described by Evander *et al.*³

No HPV DNA was detected in any of the examined individuals, regardless of their clinical history, as shown in the table. This was not because the DNA material was not sensitive to the PCR reaction as such, since with the PCR technique it was possible to detect the presence of HLA antigens, as also shown in the table. As an HPV positive control for this assay we used an HPV positive laryngeal papilloma (data not shown).

The absence of HPV DNA in PBLs of cervical carcinoma patients was unexpected, since in a recent study HPV DNA was detected in peripheral blood mononuclear cells (PBMCs) in approximately 50% of the patients suffering from urogenital HPV infections.⁴ In this previous study, the DNA used for the PCR reaction was purified from 3000 and 7500 PBMCs or purified directly from 20 µl of serum, both from healthy individuals, and from patients with urogenital infections. The patients with urogenital infections were defined as patients with HPV positivity in their cervical smears by PCR in at least two consecutive screenings. One third of these patients were also suffering from condyloma accuminatum of the vulvae. The primers used for PCR amplification corresponded to the E6 open reading frame of HPV. Using the same PCR assay HPV DNA was not detected in any of the individuals in the healthy control group.

In this present study, we have used a slightly different approach. First of all we have examined patients with a history of past or ongoing cervical cancer. Our starting material has been 8 ml of blood. DNA was prepared from the whole sample. Thus, if the virus infected cells were present in a low concentration (1 virus infected cell/10⁶-10⁷ cells), viral DNA should still have been recovered. Furthermore, although not all the extracted DNA was used in the PCR assay, since papovaviruses given an episomal viral infection, with several copies (50-200) of the virus/infected cell, viral DNA should still have been detected. This has not been the case.

The differences observed between the two studies could be due to the fact that the patient groups examined were derived from different populations, or different patient groups. Whether or not the use of different primers for the PCR reaction plays a role may be debated.

Absence of HPV DNA in PBLs of patients with cervical cancer

| Disease status: | No. of patients | HPV positive | HLA DQ positive |
|---|-----------------|--------------|-----------------|
| Progressive squamous cell carcinoma | 22 | 0/22 | 22/22 |
| Progressive adenocarcinoma | 5 | 0/5 | 5/5 |
| Non progressive squamous cell carcinoma | 9 | 0/9 | 9/9 |
| Non progressive adenocarcinoma | 7 | 0/7 | 7/7 |
| "Healthy patients"* | 8 | 0/8 | 8/8 |
| Total no. | 45 | 0/45 | 45/45 |

*Patients with a normal PAD